Criteria for Attributing Lung Cancer to Asbestos Exposure

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The article by Mollo and coworkers examines the criteria for attribution of lung cancers to asbestos exposure, suggesting that the number of asbestos-related lung cancers in Italy might be underestimated. Their review of 924 consecutive lobectomies and pneumonectomies for lung cancer in northwest Italy included light microscopic asbestos body counts for asbestos body concentration in addition to histologic examination for asbestosis and asbestos bodies. Their interpretation is that 6% of the lung cancers in their series are attributable to asbestos exposure because of histologic diagnosis of asbestosis. However, they also conclude that another 0.5% of their cases had interstitial fibrosis without asbestos bodies on histologic section but an elevated asbestos body concentration on digestion study. Mollo and coworkers raise the possibility that these cases also may be asbestos-related lung cancers.

The great majority of lung cancers are caused by tobacco smoke, but a minority of lung cancers are caused by asbestos exposure, virtually always in association with tobacco smoke exposure. One reason to identify the lung cancers caused by asbestos exposure is for establishing occupational and public health policies regarding asbestos or for investigation of lung cancer pathogenesis that, in turn, may provide a basis for new lung cancer therapies. In the individual case, the major reason to determine whether asbestos contributed to the development of a lung cancer is for purposes of compensation, which, in the United States, often is through litigation. Accurate identification of patients deserving compensation is also a primary concern of Mollo and coworkers.

Before proceeding, we should remind ourselves that risk of a disease and actually having a disease due to that risk are two different things. This is a rather simple observation, but it is important if one is addressing etiology of a disease. Risk has to do with populations studied for relative likelihood of disease due to a common factor not present in a control population. Any members of the at-risk population may not develop the disease under investigation and may have many individual factors that may modify the risk from the studied factor, be a confounding factor for the risk factor under study, or put them at risk for other diseases. An example can be found with the relationship of tobacco smoke to lung cancer.

A smoker has a risk of lung cancer because of smoking that is much greater than that of individuals who have never smoked, but, even so, that person has a fairly good chance of not developing a lung cancer based on the risk seen in the population of all smokers. If that smoker does develop lung cancer, the lung cancer will be caused by the tobacco smoke and could have been avoided if the person had never smoked. If we look closer at the population of smokers with a risk of lung cancer, we can identify criteria that select those with the most risk of developing lung cancer based on the cumulative dose of tobacco smoke that they are exposed to and to factors of individual susceptibility. However, the causal association between tobacco smoke and lung cancer is so strong that we seldom do more than obtain a smoking history and do not require a detailed analysis of corroborating evidence to link a smoker’s lung cancer to tobacco smoke in the vast majority of cases.
As rightly pointed out by Mollo et al., many studies examine only the risk of lung cancer for asbestos-exposed populations and do not investigate the criteria for ascribing an individual’s lung cancer to asbestos exposure. Studies have demonstrated that certain occupations and populations of workers commonly have higher asbestos exposures and greater risks of asbestos-related diseases than others. For compensation, however, a worker must substantiate the individual claim.

Unlike the situation with tobacco smoke and lung cancer, at least 2 factors necessitate clearly defined criteria for linking a lung cancer to asbestos in the individual case. First, most workers with asbestos exposures will not develop lung cancers, indicating that there are differences between workers and/or their asbestos exposures in regard to lung cancer risk. Second, as already noted, tobacco smoke is the primary cause of lung cancers and is sufficient by itself to cause the great majority of lung cancers. As a result, tobacco smoke exposure is a powerful confounding factor in most cases of lung cancers in workers with asbestos exposures.

In regard to the first factor, studies indicate that everyone is exposed to background levels of asbestos in the ambient air. Studies have shown that members of the general (nonoccupationally exposed) population have tens of thousands to hundreds of thousands of asbestos fibers in each gram of dry lung tissue, which translates into millions of fibers and tens of thousands of asbestos bodies in every person’s lungs. However, the general population does not have an increased risk of asbestos-related lung cancers despite these background levels. Individuals with occupational exposures to asbestos have tissue burdens of asbestos that are higher than background levels. A number of studies have failed to show an increased risk of lung cancer in populations with comparatively low levels of asbestos exposure. Therefore, the level of cumulative asbestos exposure, reported as asbestos dose or asbestos tissue burden, must be one of the factors that determine lung cancer risk. However, considering that millions of workers have had occupational exposure to asbestos and that only some of these individuals develop lung cancer, there must be other factors that separate those who develop asbestos-related lung cancer from those who do not. As with other types of exposures that carry risk of disease, including tobacco smoke, factors related to individual susceptibility also must have a role in whether an asbestos-related lung cancer develops in an individual once the requisite asbestos tissue burden is present.

The second factor creating a need for attribution criteria is the confounding factor of tobacco smoke. As previously stated, current or former active tobacco smoking accounts for 90% of all lung cancers in the United States. Secondhand environmental smoke accounts for a sizable percentage of the remainder, for a total of more than 150,000 new lung cancers in the United States each year due to tobacco smoke. In contrast, asbestos is estimated to account for 2% to 5%, or about 3,400 to 8,500 new lung cancers in the United States each year. Thus, there are anywhere from 20 to 50 tobacco-related lung cancers for every asbestos-related lung cancer. Tobacco smoke contains some 4,000 to 5,000 chemicals, including many known and suspected carcinogens, both initiators and promoters. As a result, tobacco smoke is sufficient by itself to cause the great majority of lung cancers without the additional contribution of any other agent.

Virtually all workers with lung cancers and asbestos exposure also are tobacco smokers or former smokers and, therefore, have 2 potential etiologic agents for their lung cancers. There is a synergistic effect of asbestos with tobacco smoke, and both of these potential etiologic agents are responsible for lung cancers in some workers. Other workers may have had asbestos exposure, but their lung cancers are due exclusively to their tobacco smoke exposure, like the overwhelming majority of patients with lung cancer in the general population. Specific criteria are needed to separate workers with purely tobacco-related lung cancers from those with lung cancers attributable to both tobacco and asbestos.

As noted, no increased risk of asbestos-related lung cancer from background levels of asbestos has been demonstrated in the general population, and a number of studies have failed to demonstrate an increased risk of lung cancer in populations with increased but comparatively low levels of asbestos exposure. Various tissue burden studies report thousands of asbestos bodies and millions of asbestos fibers per gram of dried lung tissue in asbestos workers with lung cancer. In industrial hygiene terms, cumulative asbestos exposure of 25 fibers per cubic centimeter year is recognized by many authorities as a minimal dose for increased risk of lung cancer. Some investigators estimate that the 25 fibers per cubic centimeter year dose doubles the risk of lung cancer. To put this in perspective, a report from Florida indicated that increased intake of dietary fat doubles the risk of lung cancer (in multiple studies there is emerging evidence that dietary fat consumption increases the risk of lung cancer). However, it should be noted that most workers with asbestos-related lung cancer have much more than the minimal asbestos dose or tissue burden and, therefore, potentially will have more than a doubling of risk. For purposes of establishing causation criteria, however, the diminishing risk with lower levels of exposure means that a worker may have had occupational exposure to asbestos but that exposure may be less than the minimal levels of asbestos required to produce an increased risk of lung cancer.

This observation has implications for some of the potential criteria that we might consider for attributing a lung cancer to asbestos exposure. Workers with asbestos-related
lung cancers usually will have histories of asbestos exposure and are expected to have asbestos bodies on tissue sections of their lung parenchyma. Many also coincidentally will have pleural plaques because of their asbestos exposure. However, asbestos bodies can be seen in tissue sections when the asbestos tissue burden is less than the minimum for lung cancer risk. Pleural plaques also can occur at asbestos concentrations less than those required for a lung cancer risk and in tissue burden studies generally are associated with average tissue burdens that are much less than those for lung cancer. As a result, the presence of 1 asbestos body on tissue sections, or even a few asbestos bodies depending on circumstances, and the presence of pleural plaques are not reliable criteria by themselves for causally linking a lung cancer to asbestos exposure on the basis of tissue burden. Either of these findings may provide evidence of an asbestos exposure but neither, by itself, quantitates the exposure. For similar reasons, a work history of asbestos exposure must be detailed and comprehensive before it can be used to estimate the asbestos dose.

Tissue burden analyses and work history analyses tell us that not everyone who has the requisite level of asbestos exposure will develop an asbestos-related lung cancer. As noted, individual susceptibility to the asbestos exposure is necessary before an individual will develop a disease from the exposure. Asbestos workers potentially are subject to the same nonasbestos risk factors and non–asbestos-related diseases to which the general population is subject. Since tobacco smoke is sufficient by itself to cause the majority of lung cancers, there is no reason that lung cancer in a tobacco-smoking asbestos worker should not be related purely to tobacco smoking. Obviously, if the worker has less than the minimal asbestos exposure to cause asbestos-related lung cancer, the cause of the lung cancer should not be an issue. However, even with sufficient dose or tissue burden of asbestos to create a risk of asbestos-related lung cancer, a tobacco smoker could have a purely tobacco-related lung cancer like most patients with lung cancer if the worker is not susceptible to the asbestos exposure.

Do we have any marker for both asbestos tissue burden and individual susceptibility to that exposure? Over the years, a number of investigators have concluded that the increased risk for lung cancer in asbestos-exposed workers occurs in workers with asbestosis. Detailed editorials and reviews of the studies supporting this conclusion have been written by several well-known authorities in the field, including Churg, Jones et al, and Weiss and will not be repeated here. It should be noted that, over the years, a great many epidemiologic studies of lung cancer risk and asbestos exposure do not provide information about presence or absence of asbestosis in the patients. An example is the classic work by Hammond et al demonstrating an increased risk of lung cancer in insulators. Interestingly, when a histopathologic review was performed of the lung cancer cases with available lung parenchyma, the insulators in Selikoff’s series with an increased risk of lung cancer from asbestos exposure above that of their smoking showed asbestosis in 100% of cases. Evaluation of studies said to support an increased risk for asbestos-related lung cancer in the absence of asbestosis have been criticized for failing to show an increased risk when cases with asbestosis are excluded from their study populations. Overall, there is a strong association between lung cancer risk and asbestos exposure with asbestosis that can be demonstrated more readily than an association with asbestos exposure without asbestosis.

However, in response to the aforementioned reviews and editorials, reviews and editorials by other authorities in the field, including Roggli et al, Abraham, Egilman and Reinert, and Banks et al, have challenged the premise that asbestosis is necessary to causally link a lung cancer to asbestos exposure, contending that a sufficient asbestos dose or tissue burden is enough evidence by itself to establish a causal link. Some of their positions are based on different conclusions from portions of the literature, but they also often are based on grounds of intuitive reasoning. Therefore, the primary debate about criteria for attributing a lung cancer to asbestos exposure has centered on whether sufficient asbestos tissue burden alone or sufficient asbestos tissue burden with accompanying asbestosis should be the criterion. As noted by Abraham, litigation has provided much of the stimulus for this “debate,” and we already have observed that criteria for establishing cause of a lung cancer are largely for purposes of compensation in the individual case. The differences between those who require and those who do not require asbestosis may appear exaggerated in the adversarial context of litigation. No one disputes that most lung cancers are caused by tobacco smoking and that some lung cancers are caused or partly caused by asbestos exposure. No one disputes that a lung cancer in a patient with asbestosis is due to asbestos exposure. The debate is what to do with patients with lung cancer with the requisite asbestos tissue burden who do not have asbestosis, especially if they also are tobacco smokers or former smokers.

An intuitive question about the requirement of asbestosis for attributing lung cancer causation was raised in an editorial by Roggli et al and then subsequently by other editorials: Since asbestos is the cause of the lung cancer, why would only patients with asbestosis have the increased risk of asbestos-related lung cancer? This question deserves further consideration.
Part of the relationship between asbestosis and lung cancer risk has to do with the dose or tissue burden of asbestos. The risk of asbestosis and the risk of asbestos-related lung cancer rise in a parallel manner with increasing tissue burden of asbestos.7,8,22 The evidence indicates that the level of asbestos exposure required for a risk of asbestosis is in the same range as that for lung cancer risk. Asbestosis, thus, is a reliable marker that the patient has been exposed to the asbestos dose or tissue burden necessary to put that patient at risk for asbestos-related lung cancer. Tissue burden alone does not fully explain why asbestosis should be the criterion for linking a lung cancer to asbestos exposure. There are a number of forms of diffuse lung fibrosis in which there is an increased risk of lung cancer, including usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF) and collagen vascular diseases such as scleroderma.23 In earlier decades, the theory was offered that asbestos-related lung cancers were so-called scar cancers as an explanation for the link between asbestosis and lung cancer risk. In regard to local “scars,” Cagle et al24 have demonstrated that scar cancers do not arise from preexisting focal scars, but rather the cancers produce the so-called scars as a desmoplastic reaction. Similarly, lung cancer is not caused by diffuse fibrosis or scarring in the lungs, but rather lung cancer is caused by the same agent, for example asbestos, that also causes the fibrosis in susceptible patients with sufficient dose. There are underlying similarities in the increased risk of lung cancer in patients with asbestosis and patients with other forms of chronic diffuse pulmonary fibrosis. It is now thought that tobacco smoking is a likely cause of UIP/IPF.25 Tobacco smoke causes a variety of molecular events and inflammatory responses in the lung tissue with release of substances such as mediators and cytokines, some of which may have roles in the pathogenesis of both the neoplastic disease and the nonneoplastic disease producing what investigators have observed for several decades as an increased risk of lung cancer in patients with UIP/IPF. Interestingly, there is an increased risk of cancers of both the lung and skin in patients with systemic scleroderma.26 These are the same tissues where the fibrosis of scleroderma most often occurs. This, too, is consistent with molecular events and inflammatory responses that have roles in the pathogenesis of both the neoplastic and nonneoplastic diseases in the lungs and the skin in scleroderma. As a result, investigators have observed for decades an increased risk of lung cancer in patients with scleroderma of the lungs.26 Similar increases of primary cancers in organs affected by sarcoidosis (lymphoid tissues, skin, liver, and lung during the first decade of follow-up) have been reported with chronic inflammation as the putative mediator of the increased risk.27 Similar to other forms of chronic diffuse pulmonary fibrosis or inflammation associated with an increased risk of lung cancer, asbestos develops when asbestos fibers stimulate inflammatory cells to produce a variety of mediators of fibrogenesis—eg, growth factors, cytokines, and oxidative damage.23,28-33 As suggested by Rom et al34 a decade ago and observed by subsequent investigators, some of these mediators also can act as similar mediators for the growth of carcinomas. A component of the individual susceptibility that I have referred to would be related, for example, to whether the individual produces the mediators, how fast or how much the individual metabolizes the mediators, and how many receptors the individual has for the mediators. The role of these mediators in both fibrogenesis and carcinogenesis provides a basis for the simultaneous occurrence of asbestosis and asbestos-related lung cancers in the same individual and a basis for the increased risk of lung cancer in patients with asbestosis. Of course, most tobacco smokers with lung cancer do not have UIP/IPF. However, there are other tobacco-related changes that can be observed more often in the lung tissue of patients with tobacco-related lung cancers. In particular, it is the subpopulation of smokers with chronic obstructive pulmonary disease who have the greatest risk of developing lung cancer, and the association of these diseases with lung cancer is so strong that emphysema and other forms of chronic obstructive pulmonary disease have been reported to be risk factors for lung cancer independent of tobacco smoking.35-38 In the case of emphysema and other smoking-related changes in the lung tissue, we once again have a situation in which various inflammatory, oxidative, and growth factor mediators have a role that might impact carcinogenesis as well as the changes in other lung tissues, including remodeling of tissue in emphysema. However, as noted, the causal association between tobacco smoke and lung cancer is so strong that we do not require identification of other tissue markers of tobacco dose and susceptibility to that dose to attribute a lung cancer to tobacco smoking. However, we still have largely been talking about risk in populations and, for assessing individuals, we would like to know how often a patient with lung cancer with the requisite level of asbestos exposure also has asbestosis. This fundamental question has been neglected in most studies, but Roggli and Sanders39 recently reported on 234 lung cancer cases with data on asbestos tissue burden from digestion studies. Their cases were mostly medicolegal cases and, therefore, expected to have at least some asbestos exposure above background. In the series of Roggli and Sanders,39 all patients with lung cancer with asbestos tissue burdens above 50,000 amphibole fibers per gram of wet lung tissue by scanning electron microscopy had histopathologic asbestosis in sections of their lung tissue except for 10 patients (based on
their Table 6), or 6.5%, of the 155 patients without asbestosis. This finding indicates that the great majority of patients with lung cancer with asbestos tissue burden sufficient to increase lung cancer risk also have asbestosis on tissue sections. This is consistent with asbestosis as a marker of asbestos-related lung cancer, both as an indicator of the requisite tissue burden for increased lung cancer risk and as verification that the individual is susceptible to the fibrogenic-carcinogenic effects of that asbestos exposure.

There are some patients in the series of Roggli and Sanders\(^39\) that have the requisite asbestos burdens for lung cancer risk but who do not have asbestosis. Do these patients have asbestos-related lung cancers or not? I do not think there is any way to really tell from the published data. Since we would expect that some people with excessive amphibole burdens would not be susceptible to those tissue burdens, we cannot say whether one, several, or all of these patients would have developed a lung cancer anyway. This is especially problematic in any who may have been tobacco smokers. Although 93% of the patients in the study by Roggli and Sanders\(^39\) for whom information was available were smokers, it is not clear whether the 10 patients with the excessive amphibole burdens but without asbestosis were smokers.

The study by Mollo et al\(^1\) in this issue of the *Journal* has some similarities to the study by Roggli and Sanders\(^39\) but it raises a different question of how to diagnose asbestosis. Generally, the number of asbestos bodies seen on tissue sections is proportionate to the total asbestos tissue burden. Of course, with relatively low tissue burdens, no asbestos bodies may be seen on tissue sections, even if the levels are above background. When someone has a tissue burden in the range seen with asbestosis and asbestos-related lung cancer, asbestos bodies should be readily identifiable in tissue sections, and, indeed, the presence of asbestos bodies on tissue sections is a component of the definition of asbestosis. The article by Mollo et al\(^1\) raises a question that there may be a number of “occult” asbestosis cases with fibrosis and elevated asbestos burden on digestion study but no asbestos bodies on tissue sections. The literature indicates that occult asbestosis, if it exists, is extremely rare—much less frequent than the 0.5% of cases for which Mollo et al\(^1\) raised the question.

One challenge in interpreting articles on asbestos-related diseases is that different investigators use different methods for determining asbestos tissue burden and report results differently, eg, asbestos bodies vs asbestos fibers, wet weight vs dry weight, and light microscopy vs electron microscopy. Some variability in ranges for different conditions is to be expected between different laboratories as well. Therefore, results must be interpreted for the methods used and the ranges established for the individual laboratory doing the study. The concentration of asbestos bodies per gram of dry tissue that Mollo et al\(^1\) use as their cutoff for a level sufficient to produce asbestosis is lower than what others have reported, and Mollo et al\(^1\) concur with this in the article. I wonder if Mollo et al considered that some of the fibrosis in their cases might be from causes other than occult asbestosis. Churg,\(^5\) Roggli and Pratt,\(^40\) Egilman and Reinhardt,\(^29\) and Hammar\(^41\) all have pointed out potential pitfalls in the histopathologic diagnosis of asbestosis. There are many causes of lung fibrosis, and patients with lung cancer are subject to fibrosis from a variety of reasons related to their lung cancer. Lung cancers, of course, can cause peritumoral and postobstructive pneumonias or other reactions that result in interstitial fibrosis. Most of the patients in the study by Mollo et al\(^1\) were smokers, and tobacco smoke can cause smoker’s bronchiolitis and fibrosis around bronchioles and may even cause respiratory bronchiolitis—associated interstitial lung disease, desquamative interstitial pneumonia, or Langerhans histiocytosis (eosinophilic granuloma) in some patients.\(^25\)

Banks et al\(^21\) pointed out that traditional epidemiologic studies may not convince all authorities that asbestosis is required to link a lung cancer to asbestos exposure. There also are differences in whether traditional studies of various types include all the information one would like to answer specific questions. Not only are there differences in reporting results owing to varying methods within the same discipline, as already noted, there are also differences in what can be determined within different disciplines (radiologic studies may sometimes not detect the lesions of minimal grade 1 asbestosis that can be seen under the light microscope, for example). If the increased lung cancer risk occurs in workers with asbestosis, then any study that includes workers with asbestosis is expected to show an increased risk of lung cancer, even if the parameter studied is asbestos dose or tissue burden. When comparing results between asbestos studies, these factors must be taken into account, in addition to usual issues such as cohort size and control of confounding factors. As Banks et al\(^21\) point out, a molecular marker likely would be a superior tool to link lung cancers to asbestos exposure. In the case of tobacco smoke and lung cancer, the association is so strong that no special criteria are required to link a lung cancer to tobacco smoke. However, many mutations caused by tobacco smoke during the pathogenesis of lung cancer have been identified, and some of these are unique enough and frequent enough that they can be used as a “fingerprint” to demonstrate the link between a lung cancer and tobacco smoke. I agree with Banks et al\(^21\) that what is needed is a molecular marker that is unique to asbestos, or at least not caused by tobacco smoke, that would allow us to link a lung cancer to asbestos exposure. So far, molecular markers like p53 and k-ras seen in patients with...
smoking-related cancers have been reported in lung cancers said to be due to asbestos, but a unique marker for asbestos-related lung cancer has not been identified.42

From the point of view of the pathologist, asbestosis is an unambiguous marker not only of a tissue burden of asbestos sufficient to cause a risk of lung cancer but also of individuals whose tissues are susceptible to the effects of that tissue burden. Asbestosis is the most consistent marker of asbestos-related lung cancer in the literature to date and has a basis in current molecular theories of disease similar to many other inflammatory or fibrotic diseases associated with an increased risk of lung cancer, including diseases caused by tobacco smoke. Tobacco smoke is sufficient by itself to cause the vast majority of lung cancers and is sufficient by itself to cause lung cancers in workers with asbestos exposures. Asbestosis establishes the link between a lung cancer and asbestos exposure even when the patient also was a tobacco smoker. Since there is no other marker, for example, a molecular genetic marker, available to link a lung cancer to asbestos exposure, currently there is no basis in the absence of asbestosis for assuming that an individual lung cancer is caused by asbestos or asbestos and tobacco smoke combined rather than by tobacco smoke alone. This also applies to the 0.5% of cases in which Mollo et al.1 raise the issue of occult asbestosis, to which we must add a debate about the histopathologic definition of asbestosis. Unless and until a better marker comes along, the only consistently reliable marker for an asbestos-related lung cancer is asbestosis, especially in asbestos workers who are also tobacco smokers.

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References


